

KETO CANNABINOID S WITH THERAPEUTIC INDICATIONS

Cross Reference to Related Applications

- This application claims the benefit of United States Provisional Application No. 5 60/405,608, filed 8/23/2002 and United States Provisional Application No. 60/405,940, filed 8/26/2002, the contents of each of which are incorporated by reference in their entirety.

Statement Regarding Federally Sponsored Research or Development

- 10 This invention was made with U.S. Government support under Contract No. DA3801 and DA7215 awarded by the National Institute of Health. The U.S. Government has certain rights in the invention.

Field of the Invention

- 15 This invention relates generally to cannabinoid compounds. One embodiment of the present invention more particularly relates to cannabinoid compounds exhibiting fluorescence properties, particularly in the ultraviolet-visible wavelength ranges.

20 Background of the Invention

The classical cannabinoid Δ^9 -Tetrahydrocannabinol (Δ^9 -THC) is the major active constituent extracted from *Cannabis sativa*. The effects of this, and other, cannabinoids are due to an interaction with specific, high-affinity receptors. Presently, two cannabinoid receptors have been characterized: CB1 and CB2.

- 25 Characterization of these receptors has been made possible by the development of specific synthetic ligands such as the agonists WIN 55212-2 and CP 55,940.

Additionally, recent scientific discoveries have demonstrated that the endocannabinoid system is very extensive and is currently under intense investigation. Radiochemical methods have been in use for more than a decade for 30 studying the complex phenomena associated with the endocannabinoid system and cannabimimetic molecules. Despite the usefulness and sensitivity of radiochemical methods, the use of alternative methods such as fluorescence techniques can provide information not readily accessible by conventional radiochemical methods

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and circumvent certain drawbacks associated with them, such as high cost, special precautions in handling and disposal and potential health hazards. Fluorescent approaches provide great advantages over radiochemical methods in accuracy, sensitivity, efficiency, safety and a wide scope of additional applications, and
5 generally are less costly than radiochemical methods. The state-of-art fluorescence approaches enable researchers to detect particular components of complex biomolecular assemblies, including living cells. In particular the emission spectrum of a fluorescer is sensitive to its environment. Therefore, fluorescence approaches are extremely useful in providing spatial, dynamic and temporal information about the
10 interactions between macromolecules and their ligands.

With the help of available fluorescent ligands, fluorescence techniques have successfully been applied to study the behavior of a number of biological macromolecules, including dopamine receptors, histamine receptors, muscarinic receptors, adrenergic receptors, glucagon receptors, opiate receptors, adenosine
15 receptors and serotonin receptors. The applications of receptor-specific fluorescent ligands are considerably broad, such as molecular studies on ligand-induced conformational changes within the receptor, rapid kinetics of ligand-receptor interactions, the localization of the ligand-binding site on the receptor and distances between different binding sites on the same receptor. Moreover, fluorescent ligands
20 have been successfully used for studying the mobility of some receptors in both normal and pathophysiological conditions by fluorescence photobleach recovery techniques, and to localize receptors at tissue and cellular level by fluorescence microscopic techniques. Furthermore, receptor-specific fluorescent ligands have been employed for receptor assays including the determination of the receptor
25 dissociation constant (K_D) and the total receptor content of the tissue (B_{max}) by fluorescence titration techniques.

In general, fluorescent ligands are prepared by linking parent ligands with fluorescent moieties to make the newly formed ligands detectable or measurable by fluorescence techniques. Such strategies often face the challenge of reduced
30 potency or efficacy of the parent ligands during interaction with target macromolecules. The inventors are not aware of cannabinoid compounds having fluorescence properties.

Summary of the Invention

One aspect of the present invention comprises compounds exhibiting fluorescent properties. The fluorescent compounds described in compound formulas I and II are typically endogenously fluorescent and do not rely on linking the 5 cannabinoid compound to a fluorescent moiety. At present, the inventors believe that the compounds described in the compound formulas will have fluorescent properties as long as a long conjugation system (typically comprising the phenyl A ring and a double bond as well as a carbonyl group) can be formed within the tricyclic cannabinoid structure and the Y moiety comprises an electron rich structural element 10 such as nitrogen and oxygen. Some fluorescent cannabinoids not only are capable of generating strong fluorescence, but also can act as high affinity modulators for cannabinoid receptors, and are therefore, of potential usefulness as therapeutic agents through the modulation of the CB1 and/or CB2 cannabinoid receptors.

Another aspect of the present invention comprises compounds exhibiting 15 cannabimimetic activity, both fluorescent and non-fluorescent, pharmaceutical preparations employing these compounds and methods of administering therapeutically effective amounts of these compounds to provide a physiological effect.

Yet another aspect of the invention comprises methods of utilizing the 20 fluorescent compounds.

The novel fluorescent cannabinoid compounds exhibit strong fluorescence, for example in the ultraviolet-visible wavelength ranges. The emission wavelength of some of the inventive compounds ranges from about 390 nm to about 502 nm.

The molar extinction constants for some of the inventive compounds ranges from 25 about 1.5×10^4 to about 2.34×10^4 (1/Molxcm/L).

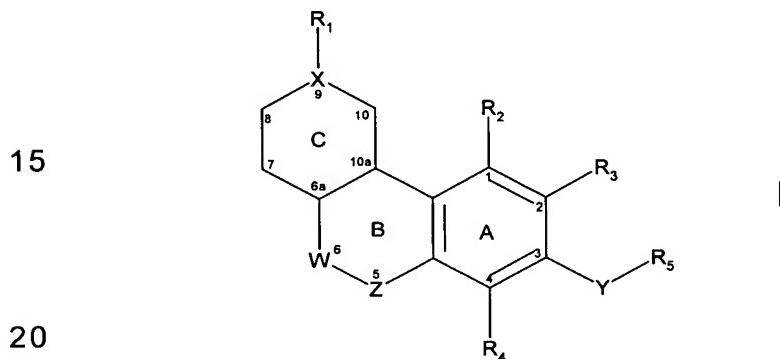
Surprisingly, the cannabinoid compounds in one aspect of the invention, comprising the A, B and C rings of the inventive structure, are intrinsically fluorescent and do not rely on linkage with a fluorescent moiety to achieve their fluorescent properties. Since these inventive fluorescent cannabinoid compounds are 30 intrinsically fluorescent, problems with reduced potency or efficacy are avoided.

In some embodiments the inventive fluorescent cannabinoids not only are capable of generating strong fluorescence, but also can act as high affinity modulators for cannabinoid receptors, and are therefore, of potential usefulness as

therapeutic agents through the modulation of the CB1 and/or CB2 cannabinoid receptors.

In general, the compositions of the invention may be alternately formulated to comprise, consist of, or consist essentially of, any appropriate components herein disclosed. The compositions of the invention may additionally, or alternatively, be formulated so as to be devoid, or substantially free, of any components, materials, ingredients, adjuvants or species used in the prior art compositions or that are otherwise not necessary to the achievement of the function and/or objectives of the present invention.

One embodiment of the invention may be represented by compound formula I, and physiologically acceptable salts thereof,



wherein:

the C ring contains one double bond.

W comprises C=O, C=S or C=CH₂. Compound formula I will have advantageous fluorescence properties when W is C=O and the C ring has a double bond in the 6a-10a position. It is believed that compound formula I will have advantageous fluorescence properties when R1 is =O and the C ring has a double bond in the 10-10a position.

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X comprises C, CH, N, S, O, SO or SO₂.

Y comprises O, S, NH, N-alkyl, N=N, C=C or C≡C.

Z comprises O, NH, N-alkyl where the alkyl group has 1 to about 5 carbon

atoms or N-substituted alkyl, where the alkyl group has 1 to about 5 carbon atoms and is substituted with at least one substituent group in any possible position.

When X is S, O, SO or SO₂, R₁ is not present.

5 When X is N, R₁ comprises H, alkyl, alkoxy-alkyl, alkylmercapto, alkylamino, SO₃alkyl, SO₂NQ₁Q₂, CONQ₁Q₂ or alkyl substituted in any possible position with at least one member selected from OH, CHO, COOH, C(halogen)₃, N₃, NCS, CN, PO₃H₂, SO₃H, or SO₃alkyl.

When X is C or CH, R₁ comprises any possible member selected from H, 10 halogen, N₃, NCS, CN, NO₂, NQ₁Q₂, =O, OQ₃, OAc, O-acyl, O-arylo, NH-acyl, NH-arylo, CHO, C(halogen)₃, COOQ₃, PO₃H₂, SO₃H, SO₃alkyl, SO₂NQ₁Q₂, CONQ₁Q₂, =CH₂, alkyl, alcohol, alkoxy, alkylmercapto, alkylamino, di-alkylamino or alkyl substituted in any possible position with at least one substituent group as later defined.

15 Q₁ and Q₂ each independently comprise H or alkyl, or
Q₁ and Q₂ together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or
Q₁ and Q₂ together comprise part of an imide ring having about 5 to 20 about 6 members.

Q₃ comprises H, alkyl, hydroxyloweralkyl, or alkyl-NQ₁Q₂.

In one advantageous variation X is C or CH and R₁ comprises any possible member selected from H, halogen, =CH₂, an alkyl group having 1 to about 5 carbon 25 atoms or an alkyl group having 1 to about 5 carbon atoms and substituted in any possible position with at least one member selected from OH, CHO, COOH, CH₂OH, halogen, C(halogen)₃, N₃, NCS, CN, PO₃H₂, SO₃H, or SO₃alkyl, SO₂NQ₁Q₂, CONQ₁Q₂, NQ₁Q₂.

30 R₂ comprises H, OH, OCH₃, OPO₃H₂, OSO₃H, PO₃H₂, SO₃H, halogen, NQ₁Q₂, COOQ₃, OQ₃, CQ₃, C(halogen)₃, alkyl-hydroxyl, NH-COalkyl, NH-COaryl, O-COalkyl, O-COalkyl-T₁, O-CO-T₁, NH-COalkyl-T₁, NH-CO-T₁, O-alkyl-T₁, O-T₁, NH-alkyl-T₁, NH-T₁, SO₃alkyl, SO₂NQ₁Q₂.

T₁ is in any possible position and comprises PO₃H, SO₃H, an alkyl group containing from 1 to about 16 carbons, tetrahydropyrrole, morpholine, thiomorpholine, piperazine, a heterocyclic ring or NQ₁Q₂;

5 T₁ may be substituted in any possible position with at least one member selected from a substituent group, OPO₃H₂, OSO₃H, PO₃H₂, a heterocyclic ring or a heteroaromatic ring;

Q₁ and Q₂ each independently comprise H or alkyl, or

4 Q₁ and Q₂ together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected 10 from O, N or S, or

10 Q₁ and Q₂ together comprise part of an imide ring having about 5 to about 6 members.

Q₃ comprises H, alkyl, hydroxyloweralkyl, or alkyl-NQ₁Q₂.

15 R₃ comprises H, OH, halogen, C(halogen)₃, CN, N₃, NCS, NQ₁Q₂ or an alkyl group having 1 to about 4 carbon atoms,

Q₁ and Q₂ each independently comprise H or alkyl, or

20 Q₁ and Q₂ together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

Q₁ and Q₂ together comprise part of an imide ring having about 5 to about 6 members.

R₄ comprises H, OH, halogen, CN, N₃, NCS, NQ₁Q₂ or an alkyl group having

25 1 to about 4 carbon atoms;

Q₁ and Q₂ each independently comprise H or alkyl, or

Q₁ and Q₂ together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

30 Q₁ and Q₂ together comprise part of an imide ring having about 5 to about 6 members.

R₅ comprises -D₁-D₂-T₂ or -D₂-T₂,

D₁, is optionally present and if present, comprises an alkyl group, a carbocyclic ring, a heterocyclic ring, N-alkyl or NH,

D₂ comprises an alkyl group having from one to about sixteen carbon atoms, a bicyclic ring, a tricyclic ring, a heterocyclic ring, an aromatic ring, a heteroaromatic ring, 1-adamantyl-T₃, 2-adamantyl-T₃, adamantan-1-ylmethyl-T₃ or adamantan-2-ylidenemethyl-T₃, alkylamino, di-alkylamino or NH

T₂ comprises, in any possible position, a substituent group as later defined or -CO-T₄,

T₃ comprises an alkyl group having from 0 to about 9 carbon atoms,

T₄ comprises H, C-(halogen)₃, OH, NH₂, alkylamino, di-alkylamino, NO₂, alkyl, alkoxy, a heterocyclic ring or a heteroaromatic ring.

In one advantageous variation R₅ comprises -D₁-D₂-T₂ or -D₂-T₂,

D₁ is optionally present and if present, comprises an alkyl, a carbocyclic ring

15 having 5 to 6 ring members, a heterocyclic ring having 5 to 6 ring members and 1,3 di-heteroatoms each independently selected from O, S, N and NH,

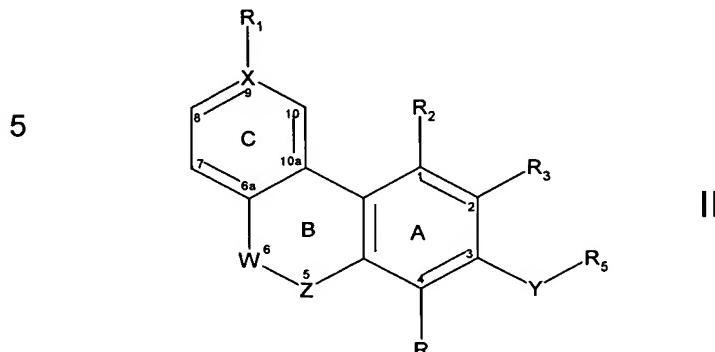
D₂ comprises an alkyl group having from one to about sixteen carbon atoms, a bicyclic ring, a tricyclic terpine, 1-adamantyl-T₃, 2-adamantyl-T₃, adamantan-1-ylmethyl-T₃ or adamantan-2-ylidenemethyl-T₃, alkylamino, di-alkylamino or NH

T₂ comprises, in any possible position, a substituent group as later defined or -CO-T₄,

T₃ comprises an alkyl group having from 0 to about 9 carbon atoms,

T₄ comprises alkyl, a heterocyclic ring or a heteroaromatic ring.

Another embodiment of the invention may be represented by compound formula II, and physiologically acceptable salts thereof,



wherein:

W comprises C=O, C=S, or C=CH₂. Advantageously, W comprises C=O. Compound formula II will have advantageous fluorescence properties when W is C=O. It is believed that compound formula II will have advantageous fluorescence properties when R1 is =O.

X comprises C, CH or N.

Y comprises O, S, NH, N-alkyl, N=N, C=C or C≡C.

20

Z comprises O, NH, N-alkyl where the alkyl group has 1 to about 5 carbon atoms or N-substituted alkyl, where the alkyl group has 1 to about 5 carbon atoms and is substituted with at least one substituent group in any possible position.

25

R₁ comprises any possible member selected from H, halogen, N₃, NCS, CN, NO₂, NQ₁Q₂, OQ₃, OAc, O-acyl, O-aryl, NH-acyl, NH-aryl, CHO, C(halogen)₃, COOQ₃, PO₃H₂, SO₃H, SO₃alkyl, SO₂NQ₁Q₂, CONQ₁Q₂, alkyl, alkyl substituted in any possible position with at least one substituent group as later defined.

Q₁ and Q₂ each independently comprise H or alkyl, or

30

Q₁ and Q₂ together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

Q₁ and Q₂ together comprise part of an imide ring having about 5 to about 6 members.

Q₃ comprises H, alkyl, alcohol, or alkyl-NQ₁Q₂.

5 In one advantageous variation R₁ comprises any possible member selected from H, halogen, OH, an alkyl group having 1 to about 5 carbon atoms or an alkyl group having 1 to about 5 carbon atoms and substituted in any possible position with at least one member selected from OH, CHO, COOH, C(halogen)₃, N₃, NCS, CN, PO₃H₂, SO₃H, or SO₃alkyl.

10 R₂ comprises H, OH, OCH₃, OPO₃H₂, OSO₃H, PO₃H₂, SO₃H, halogen, C(halogen)₃, alcohol, NQ₁Q₂, COOQ₃, OQ₃, alkyl-hydroxyl, NH-COalkyl, NH-COaryl, O-COalkyl, O-COalkyl-T₁, O-CO-T₁, SO₂NQ₁Q₂, CONQ₁Q₂, NH-COalkyl-T₁, NH-CO-T₁, O-alkyl-T₁, O-T₁, NH-alkyl-T₁, NH-T₁, SO₃alkyl, SO₂NQ₁Q₂.

15 T₁ is in any possible position and comprises PO₃H, SO₃H, an alkyl group containing from 1 to about 16 carbon atoms, tetrahydropyrrole, morpholine, thiomorpholine, piperazine, a heterocyclic ring or NQ₁Q₂;

T₁ may be substituted in any possible position with at least one member selected from a substituent group, OPO₃H₂, OSO₃H, PO₃H₂,

20 a heterocyclic ring or a heteroaromatic ring;

Q₁ and Q₂ each independently comprise H or alkyl, or

Q₁ and Q₂ together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

25 Q₁ and Q₂ together comprise part of an imide ring having about 5 to about 6 members.

Q₃ comprises H, alkyl, alcohol, or alkyl-NQ₁Q₂.

R₃ comprises H, OH, halogen, C(halogen)₃, CN, N₃, NCS, NQ₁Q₂ or C1 to C4

30 alkyl,

Q₁ and Q₂ each independently comprise H or alkyl, or

Q₁ and Q₂ together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

5 Q₁ and Q₂ together comprise part of an imide ring having about 5 to about 6 members.

R₄ comprises H, OH, halogen, C(halogen)₃, CN, N₃, NCS, NQ₁Q₂ or C1 to C4 alkyl;

Q₁ and Q₂ each independently comprise H or alkyl, or

10 Q₁ and Q₂ together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

 Q₁ and Q₂ together comprise part of an imide ring having about 5 to about 6 members.

15

R₅ comprises -D₁-D₂-T₂ or -D₂-T₂,

D₁ is optionally present and if present, comprises an alkyl, a carbocyclic ring, a heterocyclic ring, alkylamino or NH,

20 D₂ comprises an alkyl group having from one to about sixteen carbon atoms, a bicyclic ring, a tricyclic ring, a heterocyclic ring, an aromatic ring, a heteroaromatic ring, 1-adamantyl-T₃, 2-adamantyl-T₃, adamantan-1-ylmethyl-T₃, or adamantan-2-ylidenemethyl-T₃, alkylamino, di-alkylamino or NH,

T₂ comprises, in any possible position, a substituent group as later defined or -CO-T₄,

25 T₃ comprises an alkyl group having from 0 to about 9 carbon atoms,

 T₄ comprises H, C(halogen)₃, OH, NH₂, NO₂, alkyl, alkoxy, a heterocyclic ring or a heteroaromatic ring.

In one advantageous variation R₅ comprises -D₁-D₂-T₂ or -D₂-T₂

30 D₁ comprises alkylamino, di-alkylamino, NH, a carbocyclic ring having 4 to 6 ring members or a heterocyclic ring having 4 to 6 ring members and 1,3 di-heteroatoms each heteroatom independently selected from O, S and N,

 D₂ comprises an alkyl group having from one to about sixteen carbon atoms,

a bicyclic ring, a tricyclic terpine, 1-adamantyl-T₃, 2-adamantyl-T₃, adamantan-1-ylmethyl-T₃ or adamantan-2-ylidenemethyl-T₃, alkylamino, di-alkylamino or NH

T₂ comprises, in any possible position, a substituent group as later defined or -CO-T₄,

- 5 T₃ comprises an alkyl group having from 0 to about 9 carbon atoms,
T₄ comprises alkyl, a heterocyclic ring or a heteroaromatic ring.

Another embodiment of the invention may be represented by either compound formula I or II, wherein:

- 10 The C ring in compound formula I contains a double bond in the 6a-10a position.

W is C=O.

- 15 X comprises C or N.

Y comprises O, S, NH, N-alkyl, N=N, C=C, C≡C,

Z is O.

- 20 R₁ comprises OH, CH₂OH, in compound formula I; or methyl, OH, CH₂OH in compound formula II.

- 25 R₂ comprises H, OH, OCH₃, OPO₃H₂, OSO₃H, PO₃H₂, SO₃H, halogen, C(halogen)₃, alcohol, NQ₁Q₂, COOQ₃, OQ₃, NH-COalkyl, NH-CO-aryl, O-COalkyl, O-COalkyl-T₁, O-CO-T₁, NH-COalkyl-T₁, NH-CO-T₁, O-alkyl-T₁, O-T₁, NH-alkyl-T₁, NH-T₁, SO₃alkyl, SO₂NQ₁Q₂ or CONQ₁Q₂

- 30 T₁ is in any possible position and comprises PO₃H, SO₃H, an alkyl group containing from 1 to about 16 carbon atoms, tetrahydropyrrole, morpholine, thiomorpholine, piperazine, a heterocyclic ring or NQ₁Q₂; T₁ may be substituted in any possible position with at least one member selected from a substituent group, OPO₃H₂, OSO₃H, PO₃H₂, a heterocyclic ring or a heteroaromatic ring;

Q₁ and Q₂ each independently comprise H or alkyl, or

Q₁ and Q₂ together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

5 Q₁ and Q₂ together comprise part of an imide ring having about 5 to about 6 members.

Q₃ comprises H, alkyl, hydroxyloweralkyl, or alkyl-NQ₁Q₂.

R₃ comprises H, OH, halogen, C(halogen)₃, CN, N₃, NCS, NQ₁Q₂ or an alkyl

10 group having 1 to about 4 carbon atoms,

Q₁ and Q₂ each independently comprise H or alkyl, or

Q₁ and Q₂ together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

15 Q₁ and Q₂ together comprise part of an imide ring having about 5 to about 6 members.

R₄ comprises H, OH, halogen, C(halogen)₃, CN, N₃, NCS, NQ₁Q₂ or an alkyl group having 1 to about 4 carbon atoms;

20 Q₁ and Q₂ each independently comprise H or alkyl, or

Q₁ and Q₂ together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

25 Q₁ and Q₂ together comprise part of an imide ring having about 5 to about 6 members.

R₅ comprises -D₁-D₂-T₂ or -D₂-T₂,

D₁ is optionally present and if present, comprises an alkyl, a carbocyclic ring, a heterocyclic ring, alkylamino or NH.

30 D₂ comprises an alkyl group having from one to about sixteen carbon atoms, a bicyclic ring, a tricyclic ring, 1-adamantyl-T₃, 2-adamantyl-T₃, adamantan-1-ylmethyl-T₃, or adamantan-2-ylidenemethyl-T₃, alkylamino, di-alkylamino or NH.

T₂ comprises, in any possible position, a substituent group as later defined or -CO-T₄,

T₃ comprises an alkyl group having from 0 to about 9 carbon atoms,

5 T₄ comprises H, C(halogen)₃, OH, NH₂, NO₂, alkyl, alkoxy, alkylamino, di-alkylamino, a heterocyclic ring or a heteroaromatic ring.

In one advantageous variation R₅ comprises -D₁-D₂-T₂ or -D₂-T₂,

D₁ is optionally present and if present, comprises an alkyl, a carbocyclic ring having 4 to 6 ring members or a heterocyclic ring having 4 to 6 ring members and 1,3 di-heteroatoms each heteroatom independently selected from O, S and N.

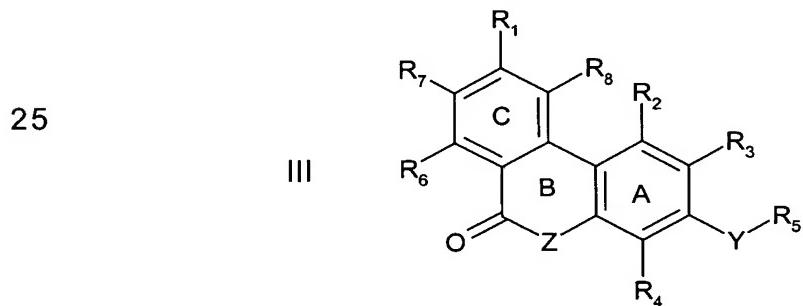
10 D₂ comprises an alkyl group having from one to about sixteen carbon atoms, alkylamino, d-alkylamino, NH, a bicyclic ring, a tricyclic ring, 1-adamantyl-T₃, 2-adamantyl-T₃, adamantan-1-ylmethyl-T₃ or adamantan-2-ylidenemethyl-T₃.

15 T₂ comprises, in any possible position, a substituent group as later defined or -CO-T₄,

T₃ comprises an alkyl group having from 0 to about 9 carbon atoms,

T₄ comprises alkyl, C(halogen)₃ aminoalkyl, di-aminoalkyl, NH₂, a heterocyclic ring or a heteroaromatic ring.

20 Another embodiment of the invention comprises compound formula III, and physiologically acceptable salts thereof,



30 wherein:

Y comprises CH₂, CH(CH₃)₂, C(CH₃)₂, a carbocyclic ring having 4 to 6 ring members or a heterocyclic ring having 4 to 6 ring members with 1 or 2 heteroatoms.

Z comprises O, S, NH, N-alkyl where alkyl comprises 1 to about 5 carbon atoms.

R₁ comprises H, halogen, N₃, NCS, CN, NO₂, NQ₁Q₂, =O, OQ₃, OAc, O-acyl, O-aryloxy, NH-acyl, NH-aryloxy, CHO, C(halogen)₃, COOQ₃, PO₃H₂, SO₃H, SO₃alkyl,
5 SO₂NQ₁Q₂, CONQ₁Q₂, =CH₂, alkyl, alcohol, alkoxy, alkylmercapto, alkylamino, di-alkylamino or alkyl substituted in any possible position with at least one member selected from the substituent groups defined later.

R₂ comprises H, OH, OCH₃, OPO₃H₂, OSO₃H, PO₃H₂, SO₃H, halogen, C-(halogen)₃, NQ₁Q₂, COOQ₃, OQ₃, NH-COalkyl, NH-COaryl, O-COalkyl, O-COalkyl-T₁,
10 O-CO-T₁, alkyl-hydroxyl, NH-COalkyl-T₁, NH-CO-T₁, O-alkyl-T₁, O-T₁, NH-alkyl-T₁, NH-T₁, SO₃alkyl, SO₂NQ₁Q₂ or CONQ₁Q₂

T₁ is in any possible position and comprises PO₃H, SO₃H, an alkyl group containing from 1 to about 16 carbons, tetrahydropyrrrole, morpholine, thiomorpholine, piperazine, a heterocyclic ring or NQ₁Q₂;

15 T₁ may be substituted in any possible position with at least one member selected from a substituent group, OPO₃H₂, OSO₃H, PO₃H₂, a heterocyclic ring or a heteroaromatic ring;

Q₁ and Q₂ each independently comprise H or alkyl, or

Q₁ and Q₂ together comprise part of a heterocyclic ring having about

20 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

Q₁ and Q₂ together comprise part of an imide ring having about 5 to about 6 members.

Q₃ comprises H, alkyl, alcohol or alkyl-NQ₁Q₂.

25 R₃, R₄, R₆, R₇, or R₈ each independently comprise H, OH, halogen, C(halogen)₃, CN, N₃, NCS, NQ₁Q₂ or an alkyl group having 1 to about 4 carbon atoms,

Q₁ and Q₂ each independently comprise H or alkyl, or

30 Q₁ and Q₂ together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

Q_1 and Q_2 together comprise part of an imide ring having about 5 to about 6 members.

R_5 comprises - D_1 - D_2 - T_2 or - D_2 - T_2 , with the below listed provisos.

5 D_1 is optionally present and if present, comprises an alkyl, a carbocyclic ring, a heterocyclic ring.

10 D_2 comprises an alkyl group having from one to about sixteen carbon atoms, alkylamino, di-alkylamino, NH, a bicyclic ring, a tricyclic ring, 1-adamantyl- T_3 , 2-adamantyl- T_3 , adamantan-1-ylmethyl- T_3 , or adamantan-2-yldenemethyl- T_3 ,

T_2 comprises, in any possible position, a substituent group as later defined, -CO- T_4 , a heterocyclic ring, a heterobicyclic ring structure, a heterotricyclic ring structure, a heteropolycyclic ring structure or a heteroaromatic ring with or without a substituent group as later defined.

15 T_3 comprises an alkyl group having from 0 to about 9 carbon atoms,

T_4 comprises H, C(halogen)₃, OH, NH₂, NO₂, alkyl, alkoxy, a heterocyclic ring or a heteroaromatic ring.

Provisos with respect to Structure Formula III:

20 When R_3 , R_4 , R_6 , R_7 and R_8 are each H; R_1 is methyl; and R_2 is OH, then Y- R_5 can not be $C(CH_3)_2(CH_2)_5CH_3$, $CH(CH_2CH_3)_2$ or $CH_2(CH_2)_3CH_3$.

 When R_3 , R_4 , R_6 , R_7 and R_8 are each H; R_1 is methyl; and Y- R_5 is n-pentyl, then R_2 can not be OCOCH₃, OCH(CH₃)COCH₃, OCH₂CH(OC₂H₅)₂ or OCH₂CHO.

25 When R_3 , R_4 , R_6 , R_7 and R_8 are each H; R_1 is bromide; and R_2 is OH, then Y- R_5 can not be n-pentyl.

 When R_1 is CH₃; R_2 is OH; and one of R_7 and R_8 is OH and the other is H, Y- R_5 can not be n-pentyl.

30 When R_3 , R_4 , R_6 , R_7 and R_8 are each H; formula III excludes compounds constructed by the combination of selecting R_1 from any of OH; OCH₃, OC₂H₅, OC₃H₇, OC₄H₉, and selecting Y- R_5 from any of (CH₂)_qCH₃, C(CH₃)₂(CH₂)_qCH₃; (CH₂)_q-C≡C; C≡C(CH₂)_q; alkyl substituted adamantyl, as

well as selecting Y from any five member ring and R₅ from (CH₂)_qCH₃, wherein q is an integer from 3-6.

In one advantageous variation, R₁ comprises halogen, C(halogen)₃, CH₂OH, 5 a substituent group as later defined, an alkyl group having 1 to about 5 carbon atoms or an alkyl group having 1 to about 5 carbon atoms and substituted in any possible position with at least one member selected from substituent groups defined later.

R₂ comprises H, OH, OCH₃, OPO₃H₂, OSO₃H, PO₃H₂, SO₃H, halogen, 10 C(halogen)₃, NQ₁Q₂, alkyl-hydroxyl, COOQ₃, OQ₃, NH-COalkyl, NH-COaryl, O-COalkyl, O-COalkyl-T₁, O-CO-T₁, NH-COalkyl-T₁, NH-CO-T₁, O-alkyl-T₁, O-T₁, NH-alkyl-T₁, NH-T₁, SO₃alkyl, SO₂NQ₁Q₂ or CONQ₁Q₂.

T₁ is in any possible position and comprises PO₃H, SO₃H, an alkyl group containing from 1 to about 16 carbons, tetrahydropyrrole, morpholine, thiomorpholine, piperazine, a heterocyclic ring or NQ₁Q₂;

15 T₁ may be substituted in any possible position with at least one member selected from a substituent group, OPO₃H₂, OSO₃H, PO₃H₂, a heterocyclic ring or a heteroaromatic ring;

Q₁ and Q₂ each independently comprise H or alkyl, or

20 Q₁ and Q₂ together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

Q₁ and Q₂ together comprise part of an imide ring having about 5 to about 6 members.

Q₃ comprises H, alkyl, alcohol, or alkyl-NQ₁Q₂.

25 R₃, R₄, R₆, R₇ and R₈ comprises H, OH, halogen, C(halogen)₃, CN, N₃, NCS, NQ₁Q₂ or an alkyl group having 1 to about 4 carbon atoms,

Q₁ and Q₂ each independently comprise H or alkyl, or

30 Q₁ and Q₂ together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

Q₁ and Q₂ together comprise part of an imide ring having about 5 to about 6 members.

R₅ comprises -D₁-D₂-T₂ or -D₂-T₂,

D₁ is optionally present and if present, comprises an alkyl group, a carbocyclic ring or a heterocyclic ring,

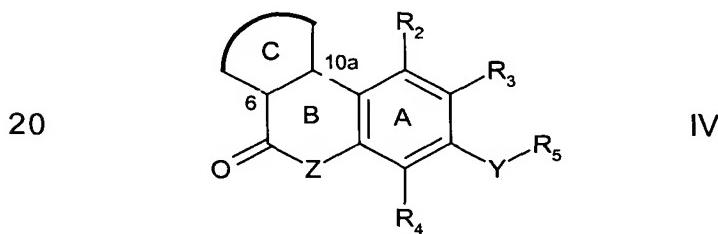
5 D₂ comprises an alkyl group having from one to about sixteen carbon atoms, alkylamino, di-alkylamino, NH, a bicyclic ring, a tricyclic ring, 1-adamantyl-T₃, 2-adamantyl-T₃, adamantan-1-ylmethyl-T₃ or adamantan-2-ylidenemethyl-T₃,

10 T₂ comprises, in any possible position, a substituent group as later defined or -CO-T₄,

T₃ comprises an alkyl group having from 0 to about 9 carbon atoms,

T₄ comprises H, C(halogen)₃, OH, NH₂, alkylamino, di-alkylamino, NO₂, alkyl, alkoxy, a heterocyclic ring or a heteroaromatic ring.

15 Another embodiment of the invention comprises compound formula IV, and physiologically acceptable salts thereof,



wherein:

25 The "C" Ring of compound formula IV comprises a carbocyclic ring, a bicyclic ring structure, a tricyclic ring structure, a heterocyclic ring, a heterobicyclic ring structure, or a heteroaromatic ring.

Y comprises CH₂, CHCH₃, C(CH₃)₂, a carbocyclic ring, an aromatic ring, a heterocyclic ring or a heteroaromatic ring,

30 Z comprises O, S, NH or N-alkyl.

R₂ comprises H, OH, OCH₃, OPO₃H₂, OSO₃H, PO₃H₂, SO₃H, halogen, C-(halogen)₃, alkyl-hydroxyl, NQ₁Q₂, COOQ₃, OQ₃, NH-COalkyl, NH-COaryl, O-COalkyl, O-COalkyl-T₁, O-CO-T₁, NH-COalkyl-T₁, NH-CO-T₁, O-alkyl-T₁, O-T₁, NH-alkyl-T₁, NH-T₁, SO₃alkyl, SO₂NQ₁Q₂ or CONQ₁Q₂.

5 T₁ is in any possible position and comprises PO₃H, SO₃H, an alkyl group containing from 1 to about 16 carbons, tetrahydropyrrole, morpholine, thiomorpholine, piperazine, a heterocyclic ring or NQ₁Q₂;

T₁ may be substituted in any possible position with at least one member selected from a substituent group, OPO₃H₂, OSO₃H, PO₃H₂, a heterocyclic ring or a heteroaromatic ring;

10 Q₁ and Q₂ each independently comprise H or alkyl, or

Q₁ and Q₂ together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

15 Q₁ and Q₂ together comprise part of an imide ring having about 5 to about 6 members.

Q₃ comprises H, alkyl, alcohol, or alkyl-NQ₁Q₂.

R₃ and R₄ each independently comprise H, OH, halogen, C-(halogen)₃, CN,

20 N₃, NCS, NQ₁Q₂ or an alkyl group having 1 to about 4 carbon atoms,

Q₁ and Q₂ each independently comprise H or alkyl, or

Q₁ and Q₂ together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

25 Q₁ and Q₂ together comprise part of an imide ring having about 5 to about 6 members.

R₅ comprises -D₁-D₂-T₂ or -D₂-T₂, with the below listed provisos.

30 D₁ is optionally present and if present, comprises an alkyl, a carbocyclic ring or a heterocyclic ring.

D₂ comprises an alkyl group having from one to about sixteen carbon atoms, alkylamino, di-alkylamino, NH, a bicyclic ring, a tricyclic ring, 1-adamantyl-T₃, 2-adamantyl-T₃, adamantan-1-ylmethyl-T₃, or adamantan-2-

ylidenemethyl-T₃.

T₂ comprises, in any possible position, a substituent group as later defined, -CO-T₄, a heterocyclic ring, a heterobicyclic ring structure, a heterotricyclic ring structure, a heteropolycyclic ring structure or a heteroaromatic ring with or without a substituent group as later defined.

T₃ comprises an alkyl group having from 0 to about 9 carbon atoms,

T₄ comprises H, halogen, OH, NH₂, NO₂, alkyl, alkoxy, a heterocyclic ring or a heteroaromatic ring, with the proviso that when the C ring is 4-methyl cyclohexane with a double bond between the 6 and 10a positions, then Y-R₅ can not be a saturated alkyl group.

10

Provisos with respect to Structure Formula IV:

When the C ring is a pyridine or N-methyl-pyridine structure having the nitrogen in the para position to the carbonyl of B ring; R₃ and R₄ are hydrogen; then Y-R₅ can not be a straight or branched alkyl chain of 1 to 20 carbon atoms.

When the C ring is 4-methyl hexane having the methyl in the para position to the carbonyl of B ring; R₃ and R₄ are hydrogen; then Y-R₅ can not be CH₂COOH or a straight or branched chain alkyl of 1 to 20 carbon atoms.

20

When the C ring is a N-methyl tetrahydropridine having a nitrogen in the para position to the carbonyl of the B ring; R₃ and R₄ are hydrogen; R₂ is OH; then Y-R₅ can not be OH, N-C₅H₁₁, CH(CH₃)(CH₂)₄CH₃, (CH₂)₁₁CH₃, or CH(cyclohexanyl).

25

When the C ring is a tetrahydropyrdine having a nitrogen in the para position to the carbonyl of the B ring; R₃ and R₄ are hydrogen; Y-R₅ is 1,2-dimethylhexanyl; R₂ is OH; then the nitrogen of C ring can not be substituted with H, CHC₆H₅, CH₃ or CH₂C≡CH.

30

When the C ring is a N-benzyl-tetrahydropridine having a nitrogen in the para position to the carbonyl of the B ring; R₃ and R₄ are hydrogen; R₂ is OH; then Y-R₅ can not be CH(CH₃)CH₂COOCH₃, CH(CH₃)CH₂COOH, CH(CH₃)CH₂COCH₃, CH(CH₃)CH₂COOH CH₂CH₃ or CH(CH₃)CH₂C(CH₃)₂OH.

Unless otherwise specifically defined, "acyl" refers to the general formula $-C(O)alkyl$.

Unless otherwise specifically defined, "acyloxy" refers to the general formula $-O-acyl$.

5 Unless otherwise specifically defined, "alcohol" refers to the general formula $alkyl-OH$ and includes primary, secondary and tertiary variations.

Unless otherwise specifically defined, "alkyl" or "lower alkyl" refers to a linear, branched or cyclic alkyl group having from 1 to about 16 carbon atoms including, for example, methyl, ethyl, propyl, butyl, hexyl, octyl, isopropyl, isobutyl, tert-butyl, 10 cyclopropyl, cyclohexyl, cyclooctyl, vinyl and allyl. The alkyl group can be saturated or unsaturated. Unless otherwise specifically limited, an alkyl group can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position. Unless otherwise specifically limited, a cyclic alkyl group includes monocyclic, bicyclic, tricyclic and polycyclic rings, for example 15 norbornyl, adamantyl and related terpenes.

Unless otherwise specifically defined, "alkoxy" refers to the general formula $-O-alkyl$.

Unless otherwise specifically defined, "alkylmercapto" refers to the general formula $-S-alkyl$.

20 Unless otherwise specifically defined, "alkylamino" refers to the general formula $-(NH)-alkyl$.

Unless otherwise specifically defined, "di-alkylamino" refers to the general formula $-N(alkyl)_2$. Unless otherwise specifically limited di-alkylamino includes cyclic amine compounds such as piperidine and morpholine.

25 Unless otherwise specifically defined, an aromatic ring is an unsaturated ring structure having about 5 to about 7 ring members and including only carbon as ring atoms. The aromatic ring structure can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position.

Unless otherwise specifically defined, "aryl" refers to an aromatic ring system 30 that includes only carbon as ring atoms, for example phenyl, biphenyl or naphthyl.

The aryl group can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position.

Unless otherwise specifically defined, "aroyl" refers to the general formula –C(=O)–aryl.

Unless otherwise specifically defined, a bicyclic ring structure comprises 2 fused or bridged rings that include only carbon as ring atoms. The bicyclic ring structure can be saturated or unsaturated. The bicyclic ring structure can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position. The individual rings may or may not be of the same type. Examples of bicyclic ring structures include, Dimethyl-bicyclo[3,1,1] heptane, bicyclo[2,2,1]heptadiene, decahydro-naphthalene and bicyclooctane.

10 Unless otherwise specifically defined, a carbocyclic ring is a non-aromatic ring structure, saturated or unsaturated, having about 3 to about 8 ring members that includes only carbon as ring atoms, for example, cyclohexadiene or cyclohexane. The carbocyclic ring can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position.

15 Unless otherwise specifically defined, "fluorescence" refers to the emission of, or the property of emitting, electromagnetic radiation by a molecule resulting from and occurring only when that molecule is excited by the absorption of radiation from some other source.

20 Unless otherwise specifically defined, "halogen" refers to an atom selected from fluorine, chlorine, bromine and iodine.

25 Unless otherwise specifically defined, a heteroaromatic ring is an unsaturated ring structure having about 5 to about 8 ring members that has carbon atoms and one or more heteroatoms, including oxygen, nitrogen and/or sulfur, as ring atoms, for example, pyridine, furan, quinoline, and their derivatives. The heteroaromatic ring can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position.

30 Unless otherwise specifically defined, a heterobicyclic ring structure comprises 2 fused or bridged rings that include carbon and one or more heteroatoms, including oxygen, nitrogen and/or sulfur, as ring atoms. The heterobicyclic ring structure is saturated or unsaturated. The heterobicyclic ring can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position. The individual rings may or may not be of the same type.

Examples of heterobicyclic ring structures include tropane, quinuclidine and tetrahydro-benzofuran.

Unless otherwise specifically defined, a heterocyclic ring is a saturated or unsaturated ring structure having about 3 to about 8 ring members that has carbon atoms and one or more heteroatoms, including oxygen, nitrogen and/or sulfur, as ring atoms, for example, piperidine, morpholine, piperazine, pyrrolidine, thiomorpholine, tetrahydropyridine, and their derivatives. The heterocyclic ring can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position.

Unless otherwise specifically defined, a heterotricyclic ring structure comprises 3 rings that may be fused, bridged or both fused and bridged, and that include carbon and one or more heteroatoms, including oxygen, nitrogen and/or sulfur, as ring atoms. The heterotricyclic ring structure can be saturated or unsaturated. The heterotricyclic ring structure can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position. The individual rings may or may not be of the same type. Examples of heterotricyclic ring structures include 2,4,10-trioxaadamantane, tetradecahydro-phenanthroline.

Unless otherwise specifically defined, a heteropolycyclic ring structure comprises more than 3 rings that may be fused, bridged or both fused and that include carbon and one or more heteroatoms, including oxygen, nitrogen and/or sulfur, as ring atoms. The heteropolycyclic ring structure can be saturated or unsaturated. The heteropolycyclic ring structure can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position. The individual rings may or may not be of the same type.

Examples of heteropolycyclic ring structures include azaadamantine, 5-norbornene-2,3-dicarboximide.

Unless otherwise specifically defined, the term "phenacyl" refers to the general formula –phenyl–acyl.

Unless otherwise specifically defined, a polycyclic ring structure comprises more than 3 rings that may be fused, bridged or both fused and bridged, and that includes carbon as ring atoms. The polycyclic ring structure can be saturated or unsaturated. The polycyclic ring structure can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position.

The individual rings may or may not be of the same type. Examples of polycyclic ring structures include adamantine, bicyclooctane, norbornane and bicyclononanes.

Unless otherwise specifically defined, a spirocycle refers to a ring system wherein a single atom is the only common member of two rings. A spirocycle can 5 comprise a saturated carbocyclic ring comprising about 3 to about 8 ring members, a heterocyclic ring comprising about 3 to about 8 ring atoms wherein up to about 3 ring atoms may be N, S, or O or a combination thereof.

Unless otherwise specifically defined, a tricyclic ring structure comprises 3 rings that may be fused, bridged or both fused and bridged, and that includes carbon 10 as ring atoms. The tricyclic ring structure can be saturated or unsaturated. The tricyclic ring structure can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position. and may be substituted or unsubstituted. The individual rings may or may not be of the same type. Examples of tricyclic ring structures include fluorene and anthracene.

15 Unless otherwise specifically limited the term substituted means substituted by a below described substituent group in any possible position. Substituent groups for the above moieties useful in the invention are those groups that do not significantly diminish the biological activity of the inventive compound. Unless otherwise specifically limited a substituent group or a substituent group that does not 20 significantly diminish the biological activity of the inventive compound includes, for example, H, halogen, N₃, NCS, CN, NO₂, NX₁X₂, OX₃, C(X₃)₃, OAc, O-acyl, O-aryl, NH-acyl, NH-aryl, NHCOalkyl, CHO, C(halogen)₃, COOX₃, SO₃H, PO₃H₂, SO₂NX₁X₂, CONX₁X₂, alkyl, alcohol, alkoxy, alkylmercapto, alkylamino, di-alkylamino, sulfonamide or thioalkoxy wherein X₁ and X₂ each independently 25 comprise H or alkyl, or X₁ and X₂ together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or X₁ and X₂ together comprise part of an imide ring having about 5 to about 6 members and X₃ comprises H, alkyl, loweralkylhydroxy, or alkyl-NX₁X₂. Unless otherwise specifically limited, a substituent group may be in any possible 30 position.

Some of the inventive cannabinoid compounds exhibit high affinity for the CB1 and/or CB2 cannabinoid receptors. Thus, another aspect of the invention is use of at least one of the inventive compounds to interact with cannabinoid receptors.

Further, some of the inventive cannabinoid compounds show a surprisingly higher selectivity for one of the cannabinoid receptors. These inventive selective compounds are able to interact with one cannabinoid receptor, for example the CB2 cannabinoid receptor, without affecting the other cannabinoid receptor to the same 5 degree. Therefore, still another aspect of the invention is use of at least one of the inventive compounds to preferentially interact with one cannabinoid receptor.

Some of the inventive compounds exhibit fluorescence properties. Therefore, still another aspect of the invention is the use of the fluorescent properties of cannabinoid compounds. In a variation, the fluorescence properties allow qualitative 10 or quantitative detection of the cannabinoid compounds and or their complex with cannabinoid receptors .

Some of the inventive fluorescent cannabinoid compounds exhibit high affinity and/or selectivity for the CB1 and/or CB2 cannabinoid receptors. Therefore, still another aspect of the invention is a method of using the inventive fluorescent 15 cannabinoid compounds as fluorescent biosensors. In some embodiments the inventive method is capable of sensing and reporting the bio-behaviors of cannabinoid receptors and molecules associated with the cannabinoid receptors through a variety of fluorescence technologies. Some applicable fluorescence technologies useful with the inventive method include, for example, Fluorescence 20 Microscopy, Fluorescence Polarization Spectroscopy, Fluorescence Resonance Energy Transfer Analysis, Flow Cytometry, Fluorescence Photo-Bleach, Immunofluorescence, and Fluorescent Competitive Binding Assay. It should be understood that the present method encompasses use of the inventive compounds in any technology wherein their fluorescent properties are desirable. Thus, the 25 inventive fluorescent cannabinoids can be employed as Fluorescent Molecular Probes, Fluorescent Imaging Agents, Fluorescent Control Standards and Cellular Markers in a broad scope of biomedical research involving cannabinoid receptors.

In addition, the fluorescent cannabinoids can be applied in clinical use as 30 Fluorescent Diagnostic Agents to determine therapeutic drug levels and the presence of drugs of abuse in fluids. The fluorescent cannabinoids can also be used as diagnostic agents for determination of white blood cells that have a high concentration of CB2 receptors.

Some of the inventive cannabinoid compounds can act as high affinity modulators for cannabinoid receptors. The inventive cannabinoid compounds therefore are potential therapeutic agents through the modulation of the CB1 and/or CB2 cannabinoid receptors.

5 Some of the novel cannabinoid compounds described herein may be cannabinoid receptor agonists. The inventive cannabinoid agonists interact with the CB1 and/or CB2 cannabinoid receptor binding site to initiate a physiological or a pharmacological response characteristic of that receptor. Therefore, a further aspect of the invention is use of at least one of the inventive compounds to initiate an
10 agonistic response from a cannabinoid receptor.

Some of the novel cannabinoid compounds described herein may be cannabinoid receptor antagonists. The inventive cannabinoid antagonists interact with the CB1 and/or CB2 cannabinoid receptor binding site to block other ligands from the receptor binding site without initiating a physiological or a pharmacological
15 response characteristic of that receptor. Thus, cannabinoid antagonists typically oppose the cannabinoid receptor site response characteristics initiated by cannabinoid agonists. Therefore, a further aspect of the invention is use of at least one of the inventive compounds to oppose initiation of an agonistic response from a cannabinoid receptor.

20 The inventive cannabinoid compounds described herein, and physiologically acceptable salts thereof, have pharmacological properties when administered in therapeutically effective amounts for providing a physiological response in individuals and/or animals. Thus, another aspect of the invention is the administration of a therapeutically effective amount of at least one of the inventive compounds, or a
25 physiologically acceptable salt thereof, to an individual or animal to provide a physiological response.

A better understanding of the invention will be obtained from the following detailed description of the article and the desired features, properties, characteristics, and the relation of the elements as well as the process steps, one with respect to
30 each of the others, as set forth and exemplified in the description and illustrative embodiments.

Description of Some Preferred Embodiments

The use of radiolabeled cannabinoid compounds in research (for example in binding assays) is well known, as are the problems with obtaining, using and disposal of radioactive compounds. The inventive fluorescent cannabinoid compounds can
5 be used to conduct research in a similar manner as radiolabeled compounds. However, fluorescent techniques such as, for example, Fluorescence Resonance Energy Transfer (FRET) can be used to assess results of the research in place of radiocounting techniques. Naturally, the inventive compounds provide benefits in procurement, handling and disposal over radioactive compounds. Additionally,
10 fluorescence techniques are highly specific and sensitive, so that the inventive compounds can provide improvements in specificity and sensitivity over radiotechniques.

Fluorescent ligands are generally useful to probe and sense receptor mechanism include the histochemical localization of receptors, their visualization on
15 cell surface, quantification of receptor mobility by the technique of fluorescence recovery after photobleaching, and fluorescent energy transfer experiments to characterize the receptor environment, e.g. the lipid bilayer in membrane or the topography of binding sites on isolated receptor molecules.

The potential applications of the inventive fluorescent cannabinoids as
20 biosensor, molecular probe, cellular marker and imaging agent can be extrapolated from numerous published works employing fluorescent ligands in other, non-cannabinoid biological system. For instance, Ariano M.A. et al described the visualization of dopamine receptors by using fluorescent ligands as imaging agents (Multiple fluorescent ligands for dopamine receptors. II. Visualization in neural
25 tissues. Brain Res. 1991 May 3;547(2):208-22), Melamed E. reported the visualization of beta-adrenoceptor in rat cerebellum via a fluorescent analogue of propranolol (Direct localisation of beta-adrenoceptor sites in rat cerebellum by a new fluorescent analogue of propranolol, Nature. 1976 Jun 3;261(5559):420-2), and Miksicek RJ et al described the imaging of estrogen receptors by a fluorescent ligand
30 (In situ localization of the estrogen receptor in living cells with the fluorescent phytoestrogen coumestrol. J Histochem Cytochem. 1993 Jun;41(6):801-10). Furthermore, applications of fluorescent compounds as molecular probes or biosensors can be exemplified by the work of McCabe RT (Characterization of

benzodiazepine receptors with fluorescent ligands, FASEB J. 1990 Aug;4(11):2934-40); Vallotton P, (Mapping The Antagonist Binding Site of The Serotonin Type 3 Receptor by Fluorescence Resonance Energy Transfer, Biochemistry, 2001 Oct 16;40(41):12237-42); Jones G, (Azole-linked coumarin dyes as fluorescence probes of domain-forming polymers, J Photochem Photobiol B. 2001 Dec 1;65(1):5-12);
5 Vallotton P et al (In Vitro and In Vivo Ligand Binding to the 5HT(3) Serotonin Receptor Characterised by Time-Resolved Fluorescence Spectroscopy, Chembiochem Europ J Chem Biol. 2001 Mar 2;2(3):205-11), Epanet RF, (Fluorescent probes of membrane surface properties, Biochim Biophys Acta, 1996
10 Oct 23;1284(2):191-5); Balice-Gordon RJ (In vivo observations of pre- and postsynaptic changes during the transition from multiple to single innervation at developing neuromuscular junctions, J Neurosci. 1993 Feb;13(2):834-55) Yamamoto T (Spectroscopic monitoring of local conformational changes during the intramolecular domain-domain interaction of the ryanodine receptor, Biochemistry, 15 2002 Feb 5;41(5):1492-501); Janssen MJ et al (A fluorescent receptor assay for benzodiazepines using coumarin-labeled desethylflumazenil as ligand, Anal Chem. 2001 Jul 1;73(13):3168-73), Guatimosim C et al (Use of fluorescent probes to follow membrane traffic in nerve terminals. Braz J Med Biol Res. 1998 Nov;31(11):1491-500), and Hazum E (Cluster formation of opiate (enkephalin) receptors in 20 neuroblastoma cells: differences between agonists and antagonists and possible relationships to biological functions, Proc Natl Acad Sci U S A. 1980 May;77(5):3038-41).

Some fluorescent compounds have also been used as diagnostic agents. For example, Cortvriendt RG et al described a method of using a non-cannabinoid 25 fluorescent compound to detect follicle density and staging in human ovarian cortical biopsy samples (Fluorescent probes allow rapid and precise recording of follicle density and staging in human ovarian cortical biopsy samples, Fertil Steril. 2001 Mar;75(3):588-93), Collins AK et al suggested a method of employing a coumarin fluorescent product as radiation dosimeter in radiation therapy (Coumarin chemical 30 dosimeter for radiation therapy, Med Phys. 1994 Nov;21(11):1741-7), and Nairn RC et al described the usefulness of fluorescent probes in monitoring cell immunity (Fluorescent probes for rapid tests of cellular immunoreactivity, Pathology. 1984 Jan;16(1):1-3).

The inventive fluorescent cannabinoids can also be used as a diagnostic tool to label and measure cells containing cannabinoid receptors. In human leukocytes, the CB2 receptors are found with particularly high abundance on B-cells, natural killer cells and macrophages. Leukocytes are the cells responsible for 5 immunosurveillance and for the specificity of immune defense in humans. The quantification of the major types of human leukocytes has proved to be of great diagnostic and prognostic value in different pathologic conditions. As one example, count of peripheral blood natural killer cells is suggested as a useful index in prognosis of large cell lymphoma (Baumann MA et al, Correlation of circulating 10 natural killer cell count with prognosis in large cell lymphoma, Cancer. 1986 Jun 15;57(12):2309-12). Typically, quantification of lymphocytes employs immuno-fluorescent antibodies as lymphocyte markers. Therefore, a potential usefulness of this invention is that at least one inventive compound can be added to white blood cells to bind to the CB2 receptors therein. Fluorescent measurement techniques can 15 be used to qualitatively and/or quantitatively assess the inventive compounds present and thereby label the cannabinoid receptors and provide information as to the quantity of receptors and white blood cells.

The inventive fluorescent cannabinoids can also be used as an imaging agent. Addition of at least one inventive compound to a tissue sample allows binding of the 20 inventive compound to receptors therein. Subsequent excitation of the bound compound/tissue sample allows image analysis of the emitted light.

As used herein a "therapeutically effective amount" of a compound, is the quantity of a compound which, when administered to an individual or animal, results in a sufficiently high level of that compound in the individual or animal to cause a 25 physiological response. The inventive compounds described herein, and physiologically acceptable salts thereof, have pharmacological properties when administered in therapeutically effective amounts for providing a physiological response useful to treat central and peripheral pain, neuropathy, neurodegenerative diseases including multiple sclerosis, Parkinson's disease, Huntington's chorea, 30 Alzheimer's disease; mental disorders such as schizophrenia and depression; to prevent or reduce endotoxic shock and hypotensive shock; to modulate appetite; to modulate the immune system; to reduce fertility; to prevent or reduce diseases associated with motor function such as Tourette's syndrome; to prevent or reduce

inflammation; to provide neuroprotection; to suppress memory; to produce peripheral vasodilation; to treat epilepsy, glaucoma, nausea associated with cancer chemotherapy as well as other ailments in which cannabinoid system is implicated.

The inventive compounds described herein, and physiologically acceptable salts thereof, have pharmacological properties when administered in therapeutically effective amounts for providing a physiological response useful to treat nausea associated with Aids wasting syndrome or to enhance appetite in AIDS wasting syndrome.

Typically, a "therapeutically effective amount" of an inventive compound is believed to range from about 5 mg/day to about 1,000 mg/day.

As used herein, an "individual" refers to a human. An "animal" refers to, for example, veterinary animals, such as dogs, cats, horses and the like, and farm animals, such as cows, pigs and the like.

The compound of the present invention can be administered by a variety of known methods, including, for example, orally, rectally, or by parenteral routes (e.g., intramuscular, intravenous, subcutaneous, nasal or topical). The form in which the compounds are administered will be determined by the route of administration. Such forms include, but are not limited to, capsular and tablet formulations (for oral and rectal administration), liquid formulations (for oral, intravenous, intramuscular, subcutaneous, ocular, intranasal, inhalation-based and transdermal administration) and slow releasing microcarriers (for rectal, intramuscular or intravenous administration). The formulations can also contain a physiologically acceptable vehicle and optional adjuvants, flavorings, colorants and preservatives. Suitable physiologically acceptable vehicles include, for example, saline, sterile water, Ringer's solution and isotonic sodium chloride solutions. The specific dosage level of active ingredient will depend upon a number of factors, including, for example, biological activity of the particular preparation, age, body weight, sex and general health of the individual being treated.

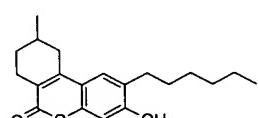
The following examples are given for purposes of illustration only in order that the present invention may be more fully understood. These examples are not intended to limit in any way the scope of the invention unless otherwise specifically indicated.

Examples:

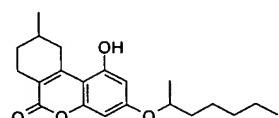
TABLE 1 illustrates some synthesized cannabinoids of the present invention (compounds 1-49). Compounds 1-27, 38 and 45-46 are representative fluorescent cannabinoids.

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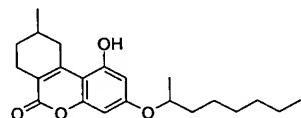
TABLE 1



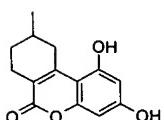
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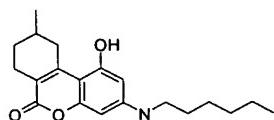
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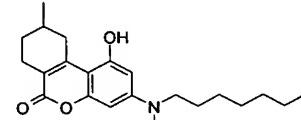
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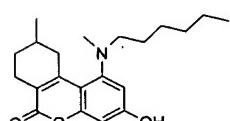
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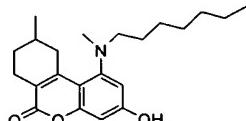
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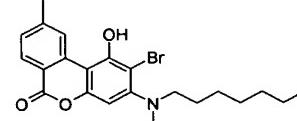
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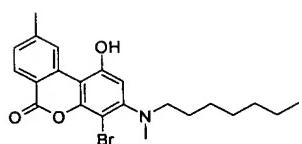
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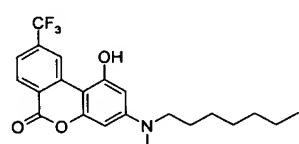
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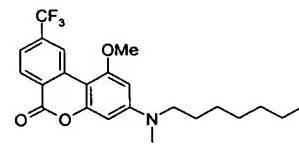
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11



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TABLE 1 (continued)

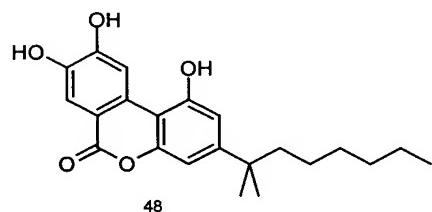
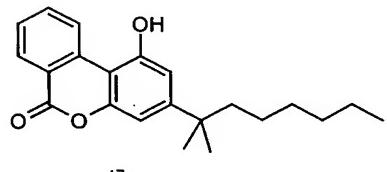
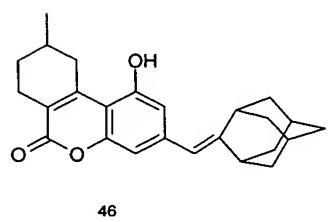
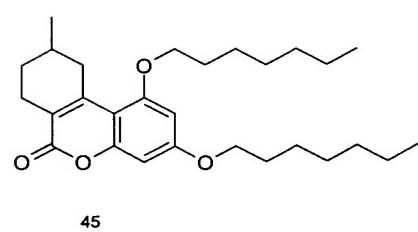
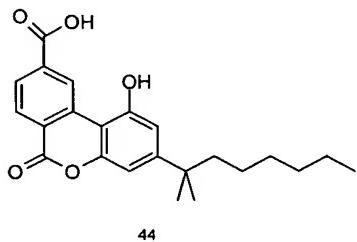
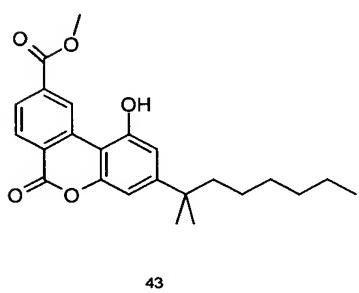
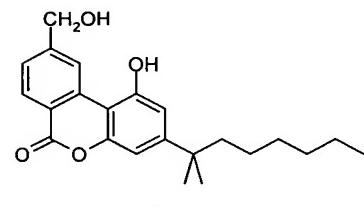
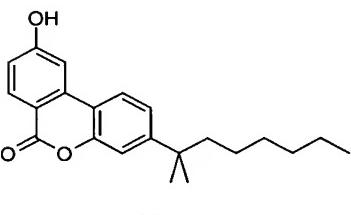
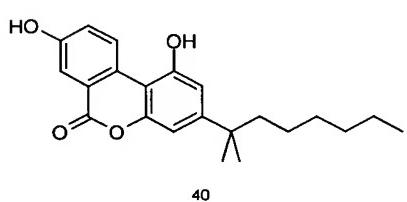
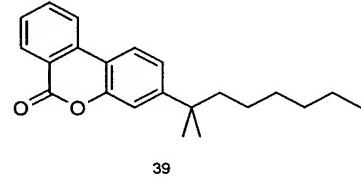
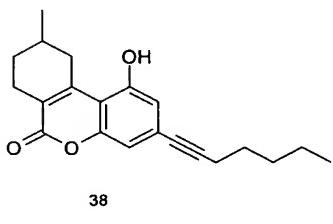
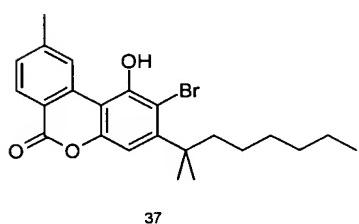
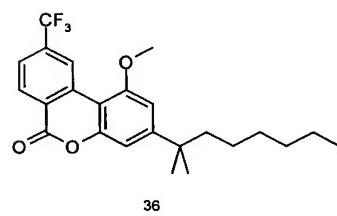
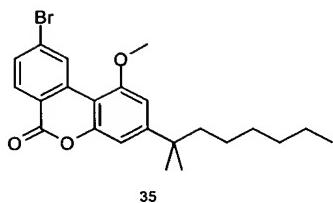
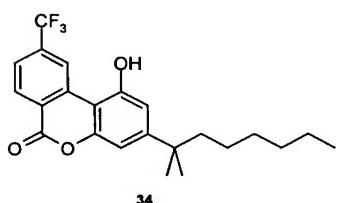
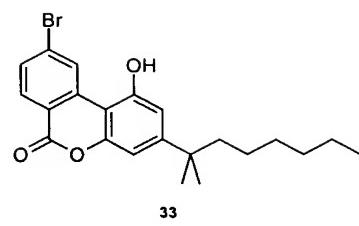
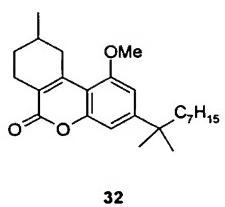
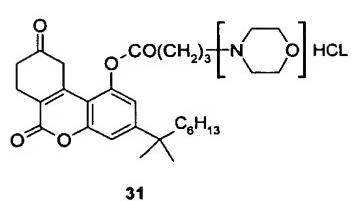
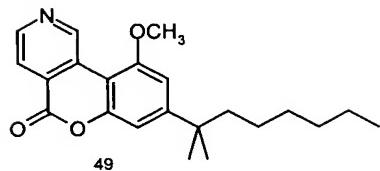


TABLE 1 (continued)



The fluorescent properties of some of the inventive compounds were examined using the following fluorescence assay protocol. All samples were processed in the same manner and diluted in JT BAKER PHOTREX Grade MeOH. Cuvettes and flasks were cleaned and rinsed with distilled water then rinsed twice with MeOH. Samples were kept in the freezer prior to testing. NSG Precision Quartz Cuvettes were used for absorption and spectral scans. Samples were diluted with methanol to a final volume of 5 mL. A 100x dilution of the samples in MeOH was performed. Absorption spectra were run using a Beckman DU-40 Spectrophotometer. Guided by absorption spectra, excitation and emission scans were run using an ISA Fluoromax-2 Fluorometer.

500 µL of MeOH was added into sample vial containing about 1 mg of testing compound, and aspirated with pipette to mix. 500 µL sample aliquot was then placed into 5 mL volumetric flask and brought up to volume with MeOH, and 5 mL was used as stock. Serial dilutions in 50 mL volumetric flasks were performed until final concentration of 100x reached. Dilution protocol was repeated for each sample. After dilution, 2.5 mL of sample was placed into a 3 mL Quartz cuvette and the cuvette was placed in ISA Fluoromax-2 Fluorometer. Absorption scan was run in Beckman DU-40 Spectrophotometer. Excitation and emission scans were run and spectral data were collected.

10 Some of the inventive fluorescent cannabinoid compounds exhibit strong fluorescence in the ultraviolet and visible wavelength ranges. Representative fluorescent data for some inventive compounds is shown in TABLE 2.

TABLE 2

compound	Absorbance Peak (nm)	Mol Extinction 1/((Mol x cm)/L)	Fluorescence Excitation Peak (nm)	Fluorescence Emission Peak (nm)	Stoke's Shift (nm)
32	327	1.50E+04	330	390	60
2	320	1.39E+04	326	423	97
5	364	1.86E+04	368	460	92
6	364	1.80E+04	367	460	93
14	405	1.14E+04	405	465	60
13	316	2.27E+04	319	519	200
16	317	2.18E+04	321	498	177
15	318	2.34E+04	320	502	182

Some of the inventive compounds were tested for CB2 receptor binding affinity and for CB1 receptor affinity (to determine selectivity for the CB2 receptor).

As used herein, "binding affinity" is represented by the K_i value which is the inhibition constant correlated with the concentration of an analog required to occupy the 50% of the total number (B_{max}) of the receptors. The lower the K_i value the higher the binding affinity. As used herein an analog is said to have "binding selectivity" if it has higher binding affinity for one receptor compared to the other receptor; e.g. a cannabinoid analog which has a K_i of 0.1 nM for CB1 and 10 nM for CB2, is 100 times more selective for the CB1 receptor.

For the CB1 receptor binding studies, membranes were prepared from rat forebrain membranes according to the procedure of P.R. Dodd et al, A Rapid Method for Preparing Synaptosomes: Comparison with Alternative Procedures, Brain Res., 107 - 118 (1981). The binding of the novel analogues to the CB1 cannabinoid receptor was assessed as described in W.A. Devane et al, Determination and Characterization of a Cannabinoid Receptor in a Rat Brain, Mol. Pharmacol., 34, 605 - 613 (1988) and A. Charalambous et al, 5'-azido Δ^8 -THC: A Novel Photoaffinity Label for the Cannabinoid Receptor, J. Med. Chem., 35, 3076 - 3079 (1992) with the following changes. The above articles are incorporated by reference herein.

Membranes, previously frozen at -80°C, were thawed on ice. To the stirred suspension was added three volumes of TME (25 mM Tris-HCl buffer, 5 mM MgCl₂ and 1 mM EDTA) at a pH 7.4. The suspension was incubated at 4°C for 30 min. At

the end of the incubation, the membranes were pelleted and washed three times with TME.

The treated membranes were subsequently used in the binding assay described below. Approximately 30 µg of membranes were incubated in silanized 5 96-well microtiter plate with TME containing 0.1% essentially fatty acid-free bovine serum albumin (BSA), 0.8 nM [³H] CP-55,940, and various concentrations of test materials in a final volume of 200 µL. The assays were incubated for 1 hour at 30 °C and then immediately filtered using Packard Filtermate 196 harvester and Whatman GF/C filterplates and washed with wash buffer (TME) containing 0.5% 10 BSA. Radioactivity was detected using MicroScint 20 scintillation cocktail added directly to the dried filterplates, and the filterplates were counted using a Packard Instruments Top-Count. Nonspecific binding was assessed using 100 nM CP-55,940. Data collected from three independent experiments performed with duplicate determinations was normalized between 100% and 0% specific binding for 15 [³H] CP-55,940, determined using buffer and 100 nM CP-55,940. The normalized data was analyzed using a 4-parameter nonlinear logistic equation to yield IC₅₀ values. Data from at least two independent experiments performed in duplicate was used to calculate IC₅₀ values which were converted to K_i values using the assumptions of Cheng et al, Relationship Between the Inhibition Constant (K_i) and 20 the concentration of Inhibitor which causes 50% Inhibition (IC₅₀) of an Enzymatic Reaction, Biochem. Pharmacol., 22, 3099-3102, (1973), which is incorporated by reference herein.

For the CB2 receptor binding studies, membranes were prepared from frozen mouse spleen essentially according to the procedure of P.R. Dodd et al, A Rapid

25 Method for Preparing Synaptosomes: Comparison with Alternative Procedures, Brain Res., 226, 107 - 118 (1981) which is incorporated by reference herein. Silanized centrifuge tubes were used throughout to minimize receptor loss due to adsorption.

The CB2 binding assay was conducted in the same manner as for the CB1 binding assay. The binding affinities (K_i) were also expressed in nanomoles (nM).

30 Some of the inventive compounds illustrated in TABLE 1 showed high affinities for the CB1 and CB2 cannabinoid receptors, with CB1 K_i values as low as 6.0 nM and CB2 K_i values as low as 0.6 nM. Some of the inventive compounds show CB2/CB1 selectivity of 760 in favor of the CB2 receptor.

Table 3 illustrates CB1 and CB2 K_i values for some inventive compounds.

TABLE 3

compound	CB1 (nM)	CB2 (nM)
1	8610	5630
2	150	25
3	30	6
4	4185	1233
5	2003	1661
6	122	128
7	160	288
8	2577	824
9	50	3
10	9	0.7
11	6680	1685
12	6365	1479
13	140	16
14	1264	90
15	990	23
16	1305	148
17	304	0.4
18	8434	355
19	40	1
20	6	0.6
47	4787	6.6
48	1946	100.6
49	3758	35.4

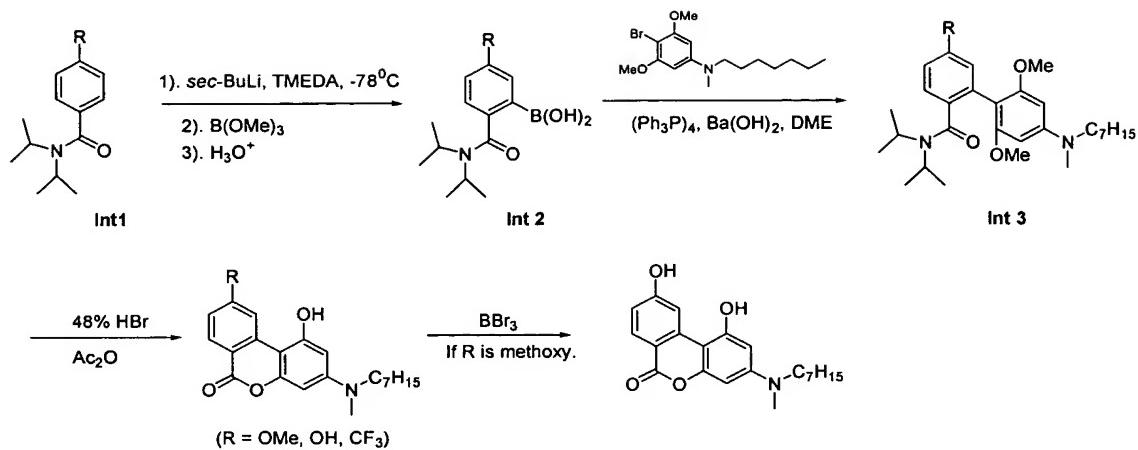
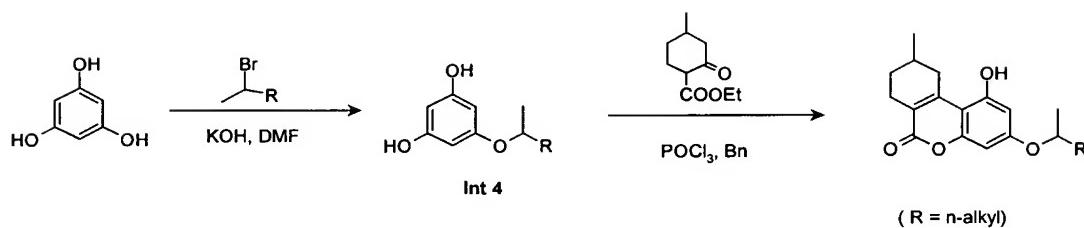
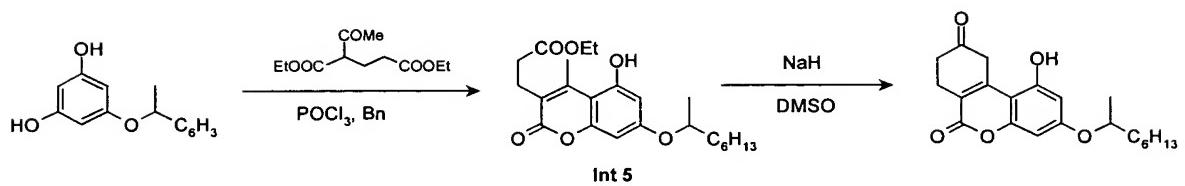
Preparation of compounds

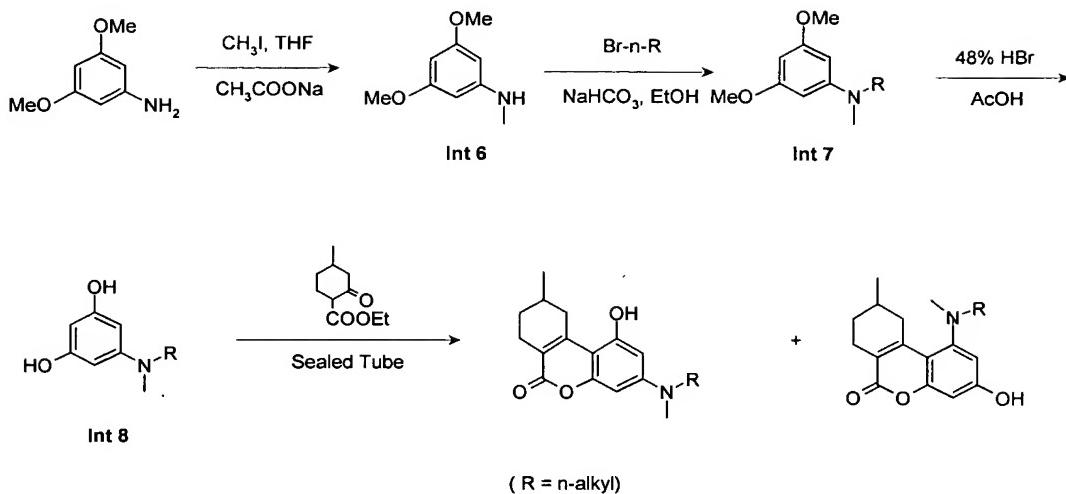
- 5 **General** All the reagents and solvents used in the following reactions are available from Sigma-Aldrich Fine Chemicals of Milwaukee, Wisconsin and/or Lancaster Synthesis Inc. of Windham, New Hampshire at the highest available grade except where indicated. All reactions were carried out under scrupulously dry conditions unless otherwise stated. Work-up organic phases are dried over Na_2SO_4 , 10 and solvents are then removed under reduced pressure. Column chromatography was carried out by using active silica gel (230–400 mesh) available from Selecto Scientific of Suwanee, Georgia. All compounds are demonstrated to be homogeneous by analytical TLC on pre-coated silica gel TLC plates (Whatman Ltd, Maidstone, Kent, England), and chromatograms are visualized by phosphomolybdic acid staining and UV lamp at wavelength of 254 nm. Structures are determined by 15

¹H NMR spectra recorded on Bruker DMX-500 MHz spectrometers and Mass spectra obtained on a Hewlett Packard HP 6890 GC-MS instrument.

The inventive compounds were prepared generally using three types of reactions, von Pechmann Condensation, Oxazoline facilitated aromatic carbon-5 carbon coupling, and Suzuki Coupling Reaction. The preparation procedures include aspects of the following references, the disclosures of which are hereby incorporated by reference.

- Alo, B.I.; Kandil, A.; Patil, P. A.; Sharp, M. J.; Siddiqui, M. A.; and Snieckus, V. Sequential Directed Ortho Metalation-Boronic Acid Cross-Coupling Reactions. A general Regiospecific Route to Oxygenated Dibenzo[b,d]pyran-6-ones Related to Ellagic Acid, *J. Org. Chem.* **1991**, 56, 3763-3768. Beak, P.; and Brown, R A., The Tertiary Amide as an Effective Director of Ortho Lithiation, *J. Org. Chem.* **1982**, 47, 34-36. Watanabe, T.; Miyaura, N.; Suzuki, A., Synthesis of Sterically Hindered Biaryls via the Palladium Catalyzed Cross-Coupling Reaction of Arylboronic Acids or their Esters with Haloarenes, *Synlett* **1992**, 207-210. Morris, S.; Mechoulam, R.; and Irene, Y., Halogenation of phenols and Phenyl ethers with Potassium Halides in the Presence of 18-Crown-6 on Oxidation with m-Chloroperbenzoic Acid, *J. Chem. Soc., Perkin Trans. 1* **1987**, 1423-1427. Rhee, M. H.; Vogel, Z.; Barg, J.; Bayewitch, M.; Levy, R.; Hanus, L.; Breuer, A.; and Mechoulam, R., Cannabinol Derivatives: Binding to Cannabinoid Receptors and Inhibition of Adenylcyclase, *J. Med. Chem.* **1997**, 40, 3228-3233. Fahrenholz, K. E., Lurie, M. and Kierstead, AR. W., The Total Synthesis of dl- Δ^9 -Tetrahydrocannabinol and Four of Its Isomers, *J. Amer. Chem. Soc.* **1967**, 89:23, 5934-5941. Love, R. Bender, P. E., Dowalo, F., Macko, E., and Fowler, P., Cannabinoids. Structure-Activity Studies Related to 1,2-Dimethylheptyl Derivatives, *J. Med. Chem* **1973**, 16, 1200-1206. Meyers, A., Reuman, M. The Synthetic Utility of Oxazolines in Aromatic Substitution, *Tetrahedron* **1985**, 41, 837-860. Novak, J., Salemink, A., Cannabis. Part 27.¹ Synthesis of 8-, 10-, and 11-Oxygenated Cannabinols, *J. Chem. Soc. Perkin Trans I.* **1983**, 2867-2871. Hattori, T., Suzuki, T., and Miyano, S., A Practical and Efficient Method for the Construction of the Biphenyl Framework; Nucleophilic Aromatic Substitution on 2-Methoxybenzoates with Aryl Grignard Reagents, *J. Chem. Soc. , Chem. Commun.* **1991**, 1375-1376.

Scheme 1**Scheme 2****Scheme 3**

Scheme 4**General Procedure for Synthesis of Compounds Prepared by Scheme 1****2-(*N,N*-Diisopropylcarboxamido)-5-alkyl/alkoxy/trifluoromethyl-phenylboronic acid (Int 2).**

Anhydrous tetrahydrofuran (250 ml) and TMEDA (9.05 ml, 60 mmol) was cooled to -78°C under argon and, with stirring, 46.2 ml (60 mmol) of 1.3 M sec-butyllithium solution was added via syringe. The yellow solution was stirred at the same temperature for about 5 minutes and a solution of 5-substituted-*N,N*-diisopropylbenzamide Int 1 (50 mmol) in 50 ml of anhydrous THF was added dropwise. The reaction mixture was stirred at -78°C for 1 hr and then 16.4 ml (150 mmol) of trimethylborate was added dropwise. The reaction mixture was allowed to warm to room temperature over night. The pH of the mixture was adjusted to about 6.5 by addition of 12% aqueous hydrochloric acid (about 50 ml) and concentrated by vacuum evaporation. The residue was extracted with dichloromethane. The combined organic extracts were dried over Na₂SO₄. Removal of solvent afforded a yellow or white form of solid product. The solid product was recrystallized in hot diethyl ether (general yield is about 95%).

N,N-Diisopropyl-5-methyl/methoxy/trifloromethyl-1'6'dimethoxy-4'-(*-N*-methyl,*N*-heptyl)-2-biphenylcarboxamide (Int 3). The above boronic acid (8 mmol), tetrakis(triphenylphosphine) palladium (0.5 mmol) and barium hydroxide octahydrate (10 mmol) and dimethoxyethane (20 ml) were mixed; 4 ml of water was
5 added and the reaction mixture was stirred at room temperature under argon for 10 min. Then, a solution of 4 mmol of the (4-Bromo-3,5-dimethoxy-phenyl)-heptyl-methyl-amine* in 10 ml of dimethoxyethane was added with stirring and the reaction mixture was stirred and refluxed under argon for 24 hr. After cooling to room temperature, the catalyst was filtered out with the facilitation of celite and the filtrate
10 was concentrated by vacuum evaporation. The residue was chromatographed on silica gel (25 % ethyl acetate in petroleum ether) to provide the product in a general yield of 50%.

*Note: (4-Bromo-3,5-dimethoxy-phenyl)-heptyl-methyl-amine was prepared via
15 bromination of Int 7: To a solution of Int 7 (800 mg, 3 mmol), tetraethylammonium chloride mono hydrate (TEACl, 20 mg)), 60 microliter anhydrous methanol in 15 ml of anhydrous dichloromethane, 0.16 ml of bromine was added dropwise at 0°C. The reaction was quenched by addition of 50 ml of 10% sodium bicarbonate aqueous solution after stirring at 0°C under argon atmosphere for 1 hr. The organic layer was
20 separated and washed quickly with water, brine, and dried over Na₂SO₄ under the protection of argon. Filtration and removal of solvent afforded the 0.97 g of the title compound, which was used directly in the reaction without further purification.

3-(*N*-methyl, *N*-heptyl)-1-hydroxy-9-methyl/methoxy/hydroxy/trifloromethyl-6*H*-25 dibenzo-[*b,d*]-pyran-6-one (13, 18, 19). 10 ml of 48% hydrobromic acid was added dropwise to the solution of 2 mmol of Int 3 in 10 ml of acetic anhydride at 0°C, then the reaction mixture was stirred and heated at 90°C for 24 hr. To obtain the 5-hydroxy product, the reaction needs to carried out for 8 more hr and the addition of 10 ml of 48% hydrobromic acid after 24 hr. The reaction mixture was then cooled
30 to room temperature and treated with 20% NaOH aqueous solution to pH about 8.5. The mixture was then extracted with ether. The ethereal solution was separated and washed with water, brine and dried over Na₂SO₄. Filtration and removal of

solvent provided yellow solid crude product. The crude was chromatographed on silica gel (40% dichloromethane-petroleum ether) to afford the expected product in a general yield of 60%.

5 **General Procedure for Synthesis of Compounds Prepared by Scheme 2**

5-(1-Methylalkyloxy)resorcinol (Int 4). To a solution of phloroglucinol (100 mmol) and potassium hydroxide (34 mmol) in 40 ml of anhydrous DMF was added 2-bromo-n-alkane (105 mmol). After stirring and heating the mixture for 16 hr at 100°C, the reaction mixture was cooled to room temperature and then treated with 25 ml of acetic acid. The reaction mixture was then filtered, and the filtrate was extracted with ethyl ether following addition of 200 ml of water, the ethereal solution was separated and washed with water thoroughly. The ethereal solution was extracted with 15% sodium hydroxide aqueous solution. The alkaline solution was separated and washed with ether, acidified with 2N HCl, and extracted with ethyl ether. The ethereal extraction was separated and washed with water, brine, and dried with Na₂SO₄. Filtration and removal of solvent provided a crude brownish product. The crude product was chromatographed on silica gel (35% acetone-petroleum ether) to afford the expected product in a general yield of 30%.

20

1-Hydroxy-9-methyl-3-(1-methyl-alkyloxy)-7,8,9,10-tetrahydro-benzo[c]chromen-6-one (2 & 3). To a stirred solution of the resorcinol **Int 4** (2 mmol) and 4-Methyl-2-oxo-cyclohexanecarboxylic acid ethyl ester (2.1 mmol) in 50 ml of anhydrous benzene was added POCl₃ (2.1 mmol) dropwise. After stirring for 2 hr at room temperature, the reaction mixture was refluxed for 20 min and allowed to stir at room temperature over night. The mixture was then treated with water and refluxed for 15 min, after which ethyl ether was added. The ethereal phase was then separated and washed with 10% NaHCO₃ aqueous solution, water, brine, and dried (Na₂SO₄). Filtration and removal of solvent provided yellow solid crude product. The crude product was chromatographed on silica gel (25% acetone-petroleum ether) to afford the expected product in a general yield of 70%.

General Procedure for Synthesis of Compounds Prepared by Scheme 3

3-[5-Hydroxy-4-methyl-7-(1-methyl-heptyloxy)-2-oxo-2H-chromen-3-yl]-propionic acid ethyl ester (Int 5). Phosphorous oxychloride (0.78 ml, 8.4 mmol) was added

- 5 to a solution of 5-(1-Methylheptyloxy)resorcinol **Int 4** (2.0 g, 8.4 mmol) and diethyl 2-acetylglutarate (2.0 g, 8.4 mmol) in 15 ml of anhydrous benzene. The reaction mixture was then refluxed at 90°C for 4 hr under argon atmosphere. The mixture was then cooled to room temperature and treated with 25 ml of water. Ethyl ether was added. The ethereal extraction was separated and washed with water, 5%
10 NaHCO₃, brine, and dried over Na₂SO₄. Filtration and removal of solvent provided 3.28 g of a yellow oily crude product. The crude product was chromatographed on silica gel (25% acetone-petroleum ether) to afford the expected product 0.78 g (22% yield). mp 116-117°C. The product was characterized by GS-MS, and 1D and 2D-¹H NMR.

15

1-Hydroxy-3-(1-methyl-heptyloxy)-7,10-dihydro-8H-benzo[c]chromere-6,9-dione (4). To a suspension of NaH (500 mg, 7.9 mmol, 60% dispersion in mineral oil,

washed several times with n-hexane) in 4 ml of anhydrous DMSO, a solution of **Int 5** (750 mg, 1.85 mmol) was added dropwise. The reaction mixture was stirred at
20 room temperature over night. The reaction mixture was then poured onto ice containing 2 ml of 5% HCl. Ethyl ether was added to extract the solid crude product.

The ethereal solution was separated and washed with water, brine, and dried over Na₂SO₄. Filtration and removal of solvent provided 640 mg yellow solid crude product. The crude product was chromatographed on silica gel (33% acetone-
25 petroleum ether) to afford the expected product 340 mg (51% yield). mp 183-185°C.

The product was characterized by GS-MS, and 1D-¹H NMR.

General Procedure for Synthesis of Compounds Prepared by Scheme 4

- 30 **(3,5-Dimethoxy-phenyl)-methyl-amine (Int 6).** A solution of 3,5-dimethoxyaniline (13.8g, 90 mmol), Iodomethane (12.7g, 90 mmol), and sodium acetate (7.4 g, 90 mmol) in 100 ml of anhydrous THF was stirred under nitrogen atmosphere for 10 hr.

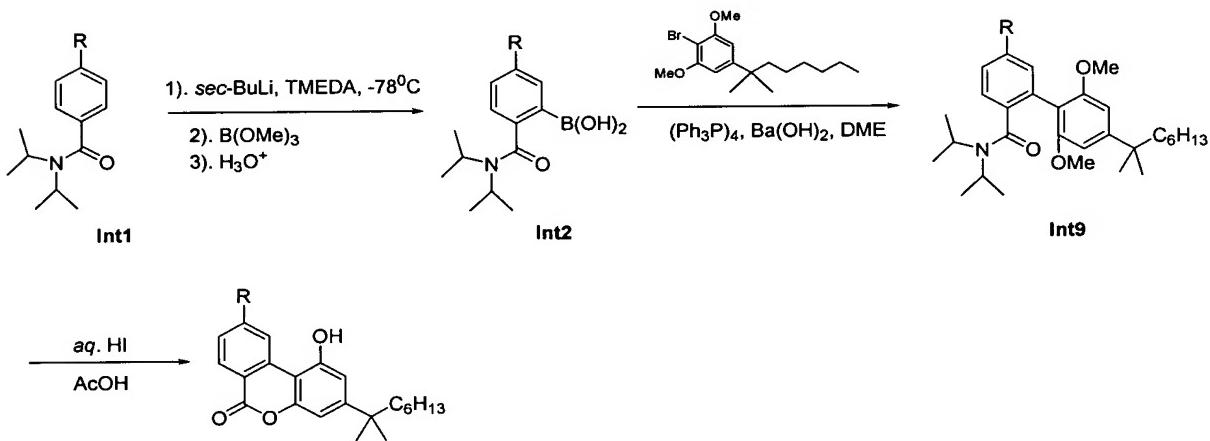
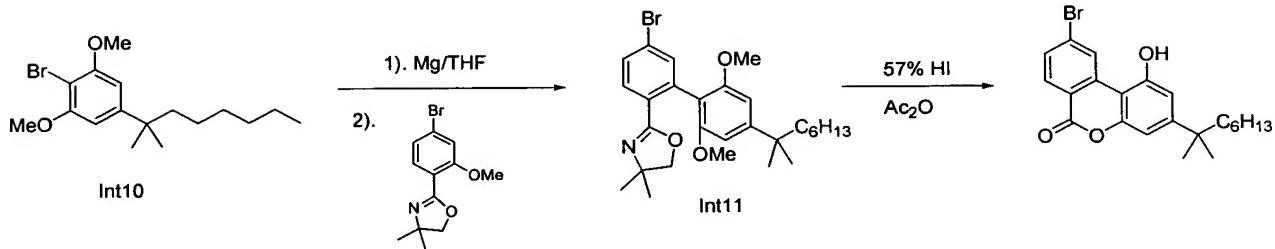
Then, THF was removed by rotary evaporation. The crude product was partitioned between water and ethyl ether. The ethereal extraction was separated and washed with water, brine, and dried over Na_2SO_4 . Filtration and removal of solvent provided 13.6 g of crude product. The crude product was chromatographed on silica gel (33% acetone-petroleum ether) to afford the expected product 4.5 g (27% yield).

(3,5-Dimethoxy-phenyl)-heptyl-methyl-amine (Int 7). A solution of **Int 6** (5g, 30 mmol), n-bromo-heptane (18.6 ml, 150 mmol), sodium hydrogen carbonate (3 g, 35 mmol) in 80 ml of anhydrous ethanol was stirred and heated at 90°C for 16 hr. After cooling to room temperature, the solvent was removed by rotary evaporation. The crude product was partitioned between water and ethyl ether. The ethereal extraction was separated and washed with water, brine, and dried over Na_2SO_4 . Filtration and removal of solvent provided 7.6 g of crude product. The crude product was chromatographed on silica gel (15% acetone-petroleum ether) to afford the expected product 4.8 g (64% yield). Another intermediate, **Int 7** (3,5-dimethoxy-phenyl)-alkyl-methyl-amine), was prepared via the same procedure.

5-(Heptyl-methyl-amino)-resorcinol (Int 8). A mixture of **Int 7** (570 mg, 2.3 mmol), 48% hydrobromic acid (13.5 ml) and glacial acetic acid (13.5 ml) was heated for 2 hr under argon atmosphere. The reaction mixture was then cooled to room temperature and treated with concentrated sodium hydroxide aqueous solution to pH 6.5. The resultant mixture was then extracted with ethyl ether. The ethereal extraction was separated and washed with water, brine, and dried over Na_2SO_4 . Filtration and removal of solvent provided 550 mg of crude product. The crude product was chromatographed on silica gel (30% acetone-petroleum ether) to afford the expected product 500 mg (98% yield). Another intermediate, **Int 8** (5-(alkyl-methyl-amino)-resorcinol), was prepared via the same procedure.

3-(Alkyl-methyl-amino)-1-hydroxy-9-methyl-7,8,9,10,-tetrahydro-
30 benzo[c]chromen-6-one (9, 10, 11, 12). A solution of 2.0 mmol of 5-(*N*-methyl, *N*-alkyl amino)-resorcinol (**Int 8**) and 2.2 mmol of 4-Methyl-2-oxo-cyclohexanecarboxylic acid ethyl ester in 4 ml of anhydrous chloroform was stirred and heated at 110°C

under argon in a sealed tube for 16 hr. The reaction mixture was then cooled to room temperature. Solvent was removed by rotary evaporation. The resultant residue was chromatographed on silica gel (15% acetone-petroleum ether) to provide the two fluorescent products in a overall yield of 54%. The two isomers were characterized by GS-MS, and 1D and 2D-¹H NMR, the major product, 3-(alkyl-methyl-amino)-1-hydroxy-9-methyl-7,8,9,10-tetrahydro-benzo[c]chromen-6-one (**Int 9 or Int 10**), was collected in a general yield of 35%.

Scheme 5**Scheme 6**

- 10 Synthesis of the compounds represented by **Scheme 5** follows the similar method described in the procedures of Scheme 1. The synthesis of compounds represented by **Scheme 6** was carried out by an oxazoline facilitated aromatic carbon-carbon coupling reaction as described by Meyers, A., Reuman, M in "The Synthetic Utility

of Oxazolines in Aromatic Substitution, *Tetrahedron* **1985**, *41*, 837-860", and Novak, J., Salemink, A. in the "Cannabis. Part 27.¹ Synthesis of 8-, 10-, and 11-Oxygenated Cannabinols, J. Chem. Soc. Perkin Trans I. **1983**, 2867-2871".

While preferred embodiments of the foregoing invention have been set forth
5 for purposes of illustration, the foregoing description should not be deemed a limitation of the invention herein. Accordingly, various modifications, adaptations and alternatives may occur to one skilled in the art without departing from the spirit and scope of the present invention.